TRANSLATION OF TOXICITY DATA INTO CW AGENT TOXICITY ESTIMATES

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ABSTRACT

The focus of the Joint Service Low Level Toxicology (non-Medical) Program has been on developing data and valid methodology for predicting dose response effects to low level CWA concentrations/doses over long durations. Consistent and defendable data generated by this program will significantly reduce the error currently embedded in estimates of "toxicity". This will, in turn, provide a consistent and uniform basis for extrapolating information on health effects and potential short or long term performance decrements from exposure times and concentrations relevant to military operations. These data are essential in creating requirements criteria for detector design, personal protective gear, and decontamination levels. At present, it is now possible to provisionally extend human CW agent toxicity estimates to longer exposure durations. Toxicity estimates for exposure durations ranging from 2 to 360 minutes have been derived for six agents (GA, GB, GD, GF, VX and HD) for inhalation/ocular vapor exposures (and some limited percutaneous vapor estimates). These provisional estimates represent an extension of the exposure durations addressed by the current human estimates from Grotte-Yang (2001).

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Translation of Toxicity Data into CW Agent Toxicity Estimates

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List of CW Agents Addressed in this Briefing

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- GA (tabun)
  - Ethyl N,N-dimethylphosphoroamidocyanidate
- GB (sarin)
  - Isopropyl methylphosphonofluoridate
- GD (soman)
  - Pinacolyl methyl phosphonofluoridate
- GF (cyclosarin)
  - Cyclohexyl methylphosphonofluoridate
- VX
  - O-ethyl-S-(2-iisopropylaminoethyl)methyl phosphonothiolate
- HD (distilled mustard)
  - Bis-(2-chloroethyl) sulfide

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Main CW Agent References Used

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Grotte-Yang (2001)

Current ECBC Low-Level Toxicology Program

- GB Rat Lethality (Mioduszewski, et al (2001))
- GB Rat Miosis (Mioduszewski, et al (2002))
- GF Rat Lethality (Anthony, et al (2002))
- GF Rat Miosis (Whalley, et al (to be published))
- GB Swine Lethality and Miosis (in progress)

Historical CW Toxicology Database

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Definition of Terms

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- C — Vapor concentration (mg/m^3)
- T — Exposure duration (min)
- CT — Concentration x Time ($mg\text{-}min/m^3$)--a term of dosage
- LC_{XX} — Lethal Concentration to XX% of exposed individuals
- EC_{YY} — Effective Concentration to cause some defined effect in YY% of exposed individuals
  - YY% also includes individuals having effects greater in severity than the defining effect of the EC_{YY}
- LCT_{XX} — Lethal CT to XX% of exposed individuals
- ECT_{YY} — Effective CT to YY% to cause some defined effect in YY% of exposed individuals
  - YY% also includes individuals having effects greater in severity than the defining effect of the ECT_{YY}
- $C^n T = k$ — Toxic load equation

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Definition of Terms (Cont.)

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n	Toxic load exponent
k	Toxic load constant
k_C	Probit slope with respect to concentration
k_T	Probit slope with respect to exposure time
k_o	Fitted constant coefficient from probit analysis
Z	Normit
IH	Whole body exposure to vapor with inhalation being the primary route of exposure
PC	Percutaneous (skin) exposure to vapor or liquid agent
OC	Ocular exposure Ocular effects: either pupil shrinkage (miosis) from nerve agents or irritation from HD
MV	Minute-Volume (liters/minute)--tidal volume of air multiplied by respiratory rate

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Estimation of LC_{50} and Probit Slope from Lethality Data

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- **Probit Analysis (Landmark Work--Finney (1947))**
  - Regress normit, Z, as function of one or more factors
    - Assumption made that response (% affected) follows normal distribution
    - Response linearized by transforming % affected into corresponding normit value

% Response	0.1	1.0	2.3	5.0	10.0	15.9	50.0
Z	-3.00	-2.33	-2.00	-1.64	-1.28	-1.00	0.00
% Response	99.9	99.0	97.7	95.0	90.0	84.1	
Z	3.00	2.33	2.00	1.64	1.28	1.00	

    - How the linearized response (Z) varies as a function of the dosage can now be estimated via a least-square fit (or linear regression) of the experimental quantal data
    - Base 10 logarithms for probit analysis is convention adopted for toxicological assessments

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Example of Probit Analysis (MINITAB® Printout)

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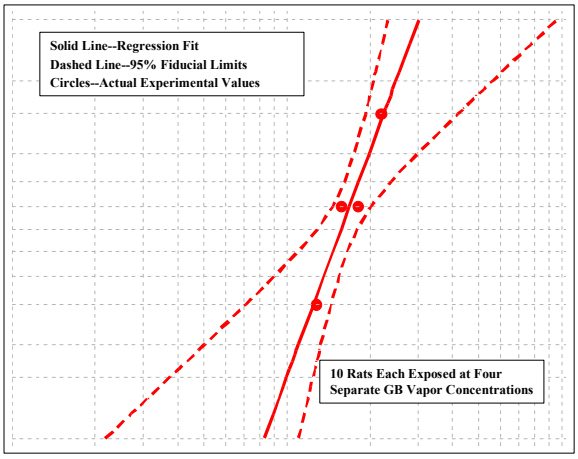

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Estimation of LC_{50} and Probit Slope from Lethality Data (Cont)

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- **Probit Analysis (cont)**
  - One factor--traditional probit analysis
    - [1] $Z = k_0 + k_C \{\log(C)\}$
      - $\log(C_{50}) = -k_0 / k_C$
      - $\log(C_{16}) = (-1 - k_0)/k_C$
  - Two or More Factors (Multifactor Probit Analysis
    - [2] $Z = k_0 + k_C \{\log(C)\} + k_T \{\log(T)\} + k_i \{X_i\} + \ldots$
      - k_i -- Probit slopes with respect to individual factors
      - Toxic load exponent is the ratio of probit slope (C) to probit slope (T)
        - $n = (k_C / k_T)$

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Dependence of Toxic Effect on Exposure Time

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Inhalation (IH) dosage defined by vapor concentration (C) multiplied by exposure time (T)

CT_{XX} -- Lethal or Effective Concentration-Time to XX% exposed

Dependence of XX% on C and T determined experimentally via probit analysis

[1] and [2] from previous slide

Exposure time dependence of CT_{XX}

Haber's Law: $CT_{XX} = k_{XX}$, with k_{XX} being a constant

Toxic Load Model

[3] $(C^nT)_{XX} = k_{XX}$ or $CT_{XX} = k_{XX}^{(1/n)} * T^{(n-1)/n}$

Using notation of [1] and [2]

[4] $(C^nT)_{XX} = \text{antilog}\{(-k_0)\, n / k_C\} * \text{antilog}\{n Z / k_C\}$

or $(C^nT)_{XX} = k_{50} * \text{antilog}\{n Z / k_C\}$

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Comparison of Functions of CT_{50} vs Time

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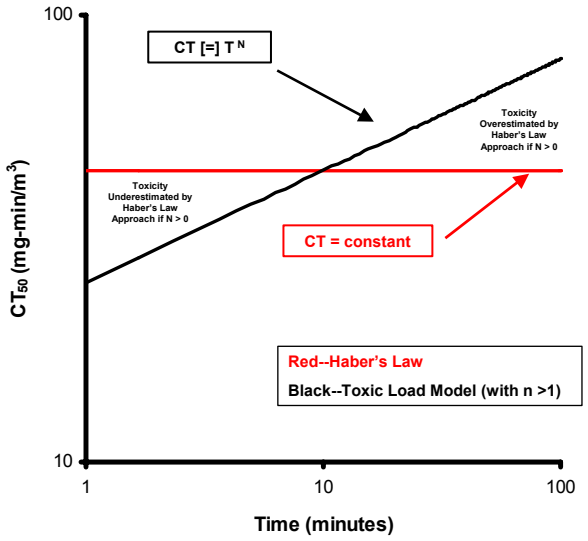
Haber's Law versus Toxic Load Model



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Comparison of GB Median Lethal Concentration-Time Values

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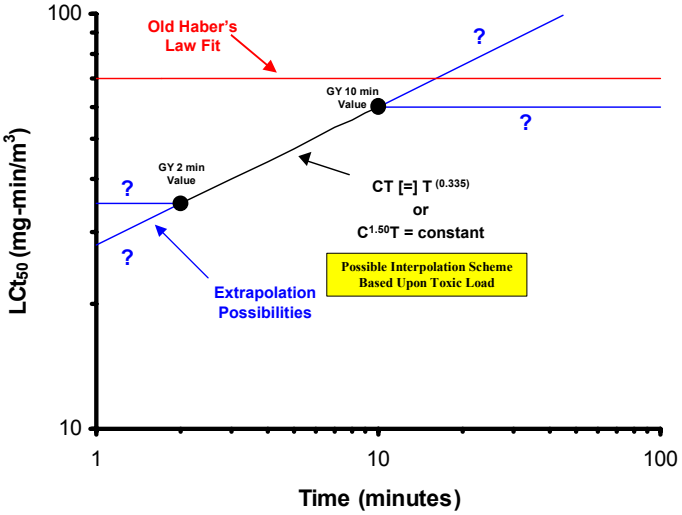
Old Haber's Law Fit vs Grotte-Yang (2001) Values for Young Adult Males



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Current CW Agent Toxicity Estimates

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- **Grotte-Yang (2001)**
  - Major assumptions
    - Acute effects (as opposed to chronic effects)
    - 70 kg, young healthy adult males
  - Agents addressed: GA (tabun), GB (sarin), GD (soman), GF (cyclosarin), VX and HD (mustard)
  - Routes of exposure addressed: IH, liquid and vapor PC, and OC

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Major Caveat--Official Disclaimer

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Starting point for the development of toxicity estimates in this briefing is Grotte-Yang (2001)

As needed, the Grotte-Yang values have been modified to acknowledge recent developments in CW agent toxicity research

Major additions/changes to Grotte-Yang reflected in this briefing

- Extending IH, PC vapor and OC (miosis or irritation) estimates beyond 2-10 minute exposures
- Modification of OC (miosis or irritation) values for exposures less than 10 minutes
- Equating probit slopes for lethality and severe effects for the G-agents

No changes made to Grotte-Yang estimates for PC vapor lethality or severe effects

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Major Caveats--Toxicity Time Dependence

- Grotte-Yang (2001) estimates are for IH exposures of 2 to 10 minutes and vapor PC exposures of 30 to 50 minutes
- Extrapolation beyond 10 minutes
  - Toxic load equation used for extrapolation
    - For exposure times longer than 10 minutes, one is the default value for toxic load exponent (n).
  - Values of n greater than one are used when experimental data exists to justify such values

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Major Caveats--Toxicity Time Dependence (Cont)

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Relationship between log CT_{XX} and log T

Assumed to be linear: the toxic load exponent (n) is constant with respect to time

Extrapolation is easier assuming log CT_{XX} versus log T is linear

Recent ECBC lethality and miosis data (GB & GF in rats) show upward curvature at longer exposure times

However, it is not known how universal such curvature will be in other mammalian species--CW agents combinations

Assuming log CT_{XX} versus log T is linear will overestimate toxicity at the longer exposure durations should upward curvature truly exist

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Major Caveats--Population Basis

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- Human toxicity estimates in this briefing are only for use with CW agent exposure scenarios involving healthy adult males
  - Evidence exists that in some mammalian species (ex. rodents) that a significant gender difference exists
  - No documented experimental (non-lethal) CW agent data available involving human females
  - Existing mammalian toxicity data comprised mainly of healthy, young adults
- To obtain toxicity estimates for the general population
  - Crosier-Sommerville (2002) gives method to convert estimates of a subpopulation (young, adult males) into those appropriate for the general population
  - General population estimates are not provided in this presentation

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Major Caveats--Population Basis (Cont.)

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For nerve agents, cases of lethality can be expected out of a pool of individuals suffering severe effects

Example: if 16 out of 100 exposed individuals experience severe effects, one to three of the 16 are likely fatalities

Put another way: an EC_{16} (severe) is roughly equivalent to an LC_{01} to LC_{02}

An EC_{50} (severe) is roughly equivalent to an LC_{10} or LC_{16}

On accompanying charts for nerve agents, an EC_{16} or ECT_{16} (severe) is plotted for comparison

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Major Caveats--Minute-Volume

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- For IH exposures, enclosed toxicity estimates assume that MV = 15 liters/min (corresponds to mild activity)
  - Toxicity needs to be adjusted for other MV values
    - At rest: MV = 10 liters/min
    - Moderate activity: MV = 40 liters/min
- Conversion of toxicity estimates for other MV values involves a linear relationship up to 50 liters/min
- Example:
  - If LC_{50} = 100 mg/m^3 at MV = 15 liters/min, then at MV = 30 liters/min, LC_{50} = (100 mg/m^3) x (15/30) = 50 mg/m^3
- For OC and PC vapor exposures, toxicity is independent of MV if respiratory protection being used

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Major Caveats--Others

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Moderate air temperatures and humidity assumed unless otherwise stated

Miosis was defined as pupil shrinkage and does not reflect presence or absence of a visual decrement

Exposed individuals are wearing light clothing

For IH exposures, personnel have no respiratory, ocular or percutaneous protection (beyond the light clothing)

For PC vapor exposures, personnel have respiratory and ocular protection, but no percutaneous protection (beyond the light clothing)

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Major Caveats--Future Toxicity Research

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- **All estimates presented in this briefing are subject to changes resulting from:**
  - New experimental animal toxicity data that are collected as part of the ECBC Low-Level Toxicology Program
  - Re-evaluation of known historical CW agent toxicity data
  - Discovery and evaluation of unpublished CW agent toxicity data

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GB IH and OC Vapor Toxicity for Human Adult Males

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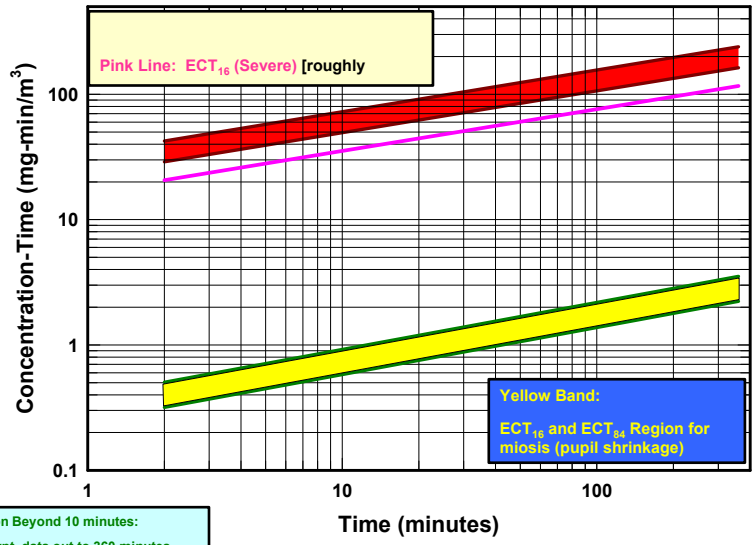
LCT_{XX} and ECT_{YY} versus Exposure Duration



Extrapolation Beyond 10 minutes:
Based on expt. data out to 360 minutes

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GA IH and OC Vapor Toxicity for Human Adult Males

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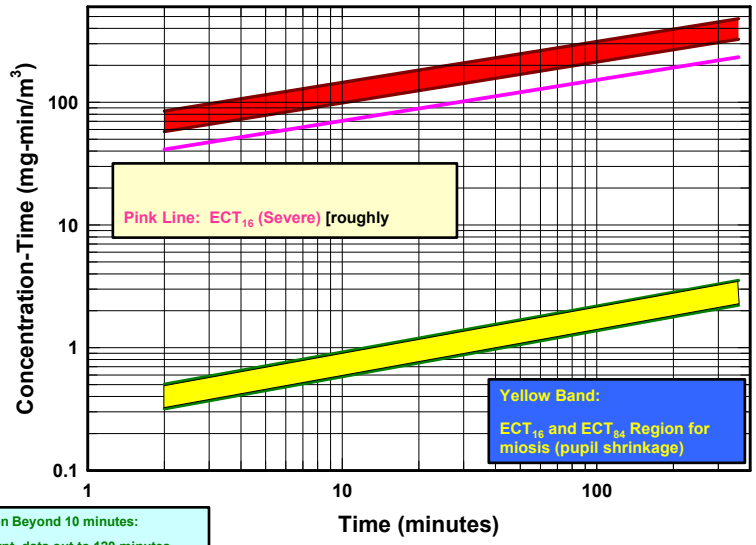
LCT_{XX} and ECT_{YY} versus Exposure Duration



Extrapolation Beyond 10 minutes:
Based on expt. data out to 120 minutes

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GD IH and OC Vapor Toxicity for Human Adult Males

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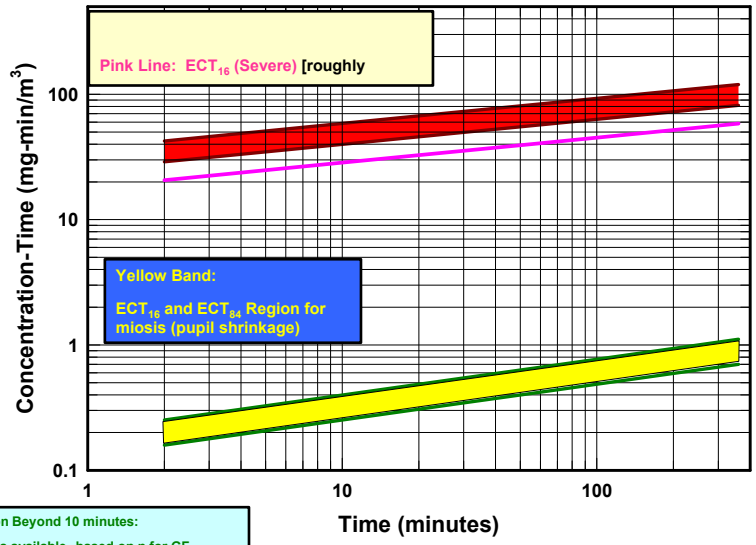
LCT_{XX} and ECT_{YY} versus Exposure Duration



Extrapolation Beyond 10 minutes:
No expt. data available--based on n for GF

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GF IH and OC Vapor Toxicity for Human Adult Males

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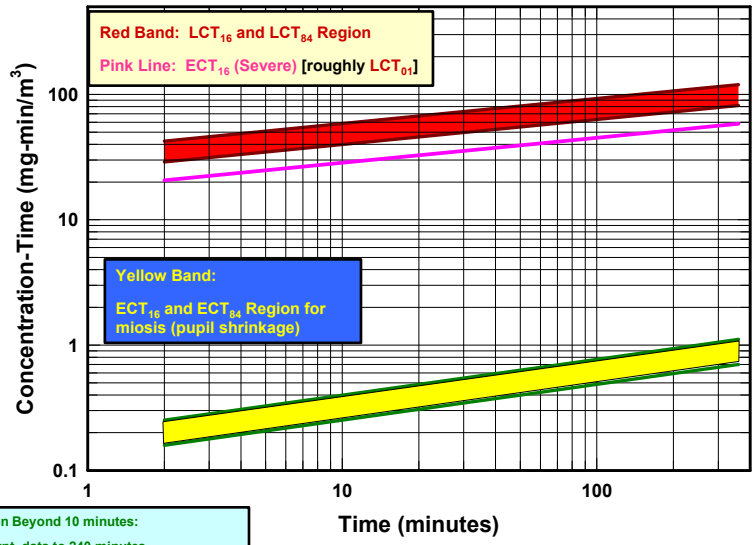
LCT_{XX} and ECT_{YY} versus Exposure Duration



Extrapolation Beyond 10 minutes:
Based on expt. data to 240 minutes

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VX IH and OC Vapor Toxicity for Human Adult Males

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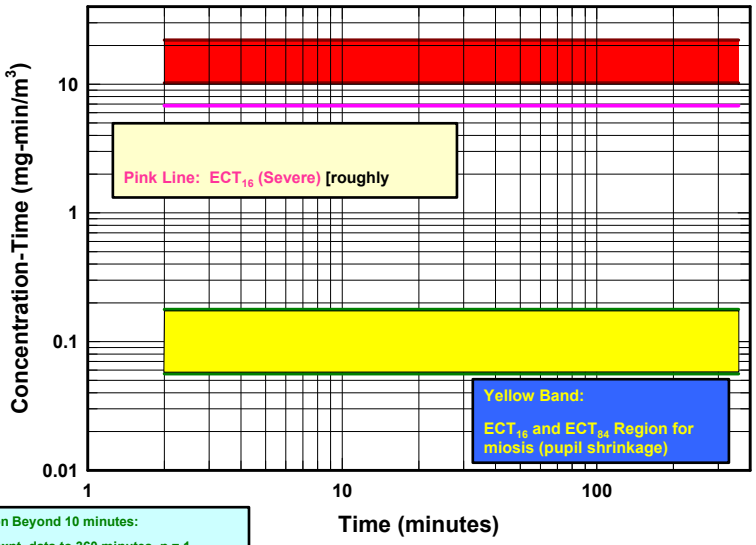
LCT_{XX} and ECT_{YY} versus Exposure Duration



Extrapolation Beyond 10 minutes:
From poor expt. data to 360 minutes, n = 1

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VX IH and PC Vapor Toxicity for Human Adult Males

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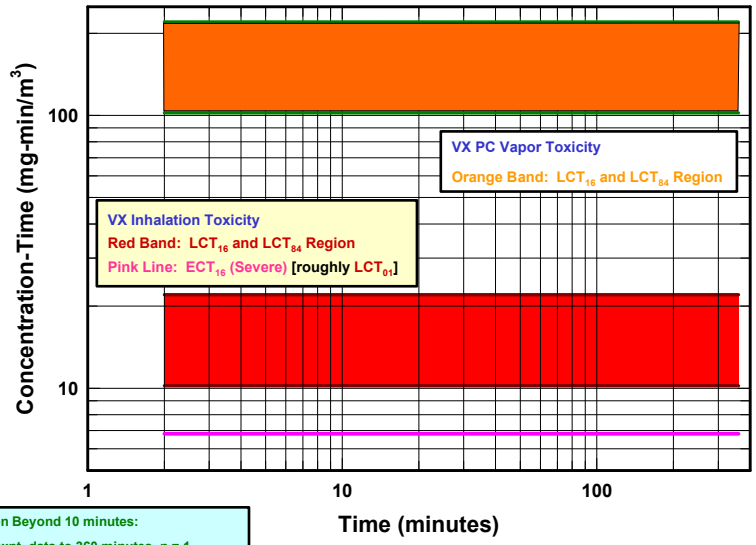
LCT_{XX} and ECT_{YY} versus Exposure Duration



Extrapolation Beyond 10 minutes:
From poor expt. data to 360 minutes, n = 1

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HD IH/PC/OC Vapor Toxicity for Human Adult Males

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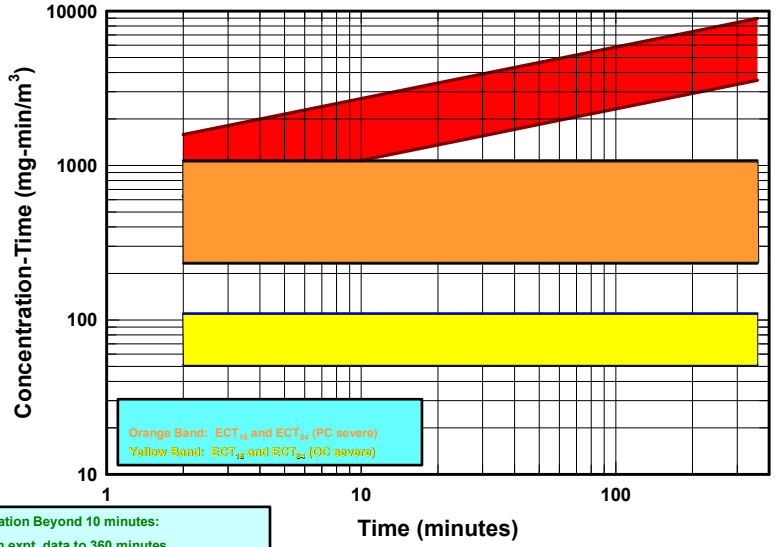
LCT_{XX} and ECT_{YY} versus Exposure Duration



Extrapolation Beyond 10 minutes:
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Summary of IH Vapor Toxicity for Human Adult Males

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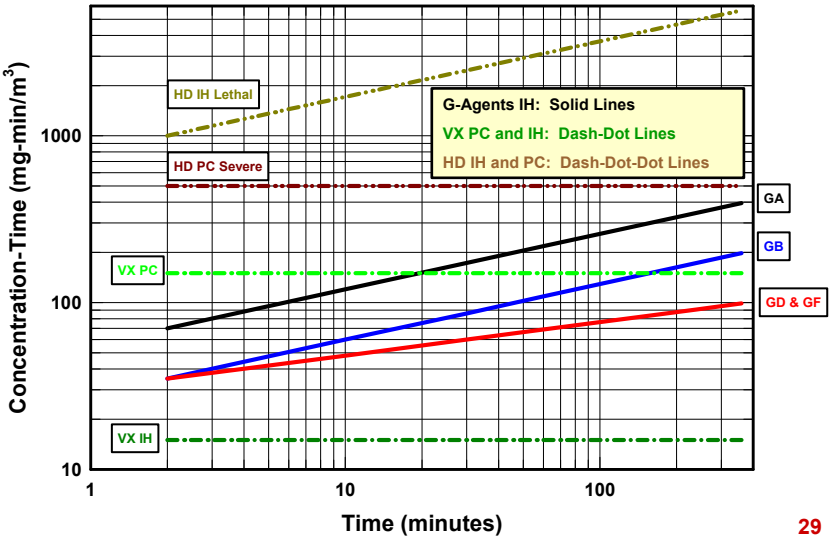
LCT_{50} and HD PC ECT_{50} versus Exposure Duration



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Summary

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Attached graphs represent ECBC's Toxicology Team's best estimate on how results from the current Low Level Toxicology Program should be used to augment the existing human CW agent toxicity values.

The estimates will be updated as new research unfolds and historical data is discovered/reanalyzed.

The point of contact for any questions concerning these estimates is the ECBC Toxicology Team.

The findings presented in this briefing are not to be construed as an official Department of the Army position unless so designated by other authorizing documents.

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